Cancer Causes and Control **10**: 583–595, 1999.

A pooled analysis of case–control studies of thyroid cancer. IV. Benign thyroid diseases

Silvia Franceschi[1,*], Susan Preston-Martin[2], Luigino Dal Maso[1], Eva Negri[3], Carlo La Vecchia[3,4], Wendy J. Mack[5], Anne McTiernan[6], Laurence Kolonel[7], Steven D. Mark[8], Kiyohiko Mabuchi[9], Fan Jin[10], Gun Wingren[11], Rosaria Galanti[12], Arne Hallquist[13], Eystein Glattre[14], Eiliv Lund[15], Fabio Levi[16], Dimitrios Linos[17] & Elaine Ron[18,*]

[1]*Servizio di Epidemiologia, Centro di Riferimento Oncologico, via Pedemontana, 33081 Aviano (PN), Italy;* [2]*Department of Preventive Medicine, University of Southern California, Los Angeles, USA;* [3]*Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy;* [4]*Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy;* [5]*Department of Preventive Medicine, University of Southern California, Los Angeles, USA;* [6]*Fred Hutchinson Cancer Research Center, Seattle, USA;* [7]*University of Hawaii at Manoa, Cancer Research Center of Hawaii, Honolulu, USA;* [8]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, USA;* [9]*Radiation Effects Research Foundation, Hiroshima, Japan;* [10]*Shanghai Cancer Institute, Shanghai, People's Republic of China;* [11]*Department of Health and Environment, Division of Occupational and Environmental Medicine, Linköping University, Linköping, Sweden;* [12]*Centrum för Tobakprevention, Huddinge, Sweden;* [13]*Stockholm Sjukhem, Stockholms, Sweden;* [14]*Cancer Registry of Norway, Montebello, Norway;* [15]*Institute of Community Medicine, University of Tromsø, Tromsø, Norway;* [16]*Registre Vaudois des Tumeurs, Lausanne, Switzerland;* [18]*Radiation Epidemiology Branch, National Cancer Institute, Rockville, USA (*Authors for correspondence)*

Received 16 November 1998; in revised form accepted 21 June 1999

Key words: goiter, hyperthyroidism, hypothyroidism, thyroid adenoma, thyroid cancer.

Abstract

Objective: To obtain more precise estimates of the association between thyroid cancer and benign thyroid diseases and to elucidate the role of potential confounders or effect modifiers.
Methods: The original data from 12 case–control studies from the United States, Asia, and Europe were pooled. Based on 2094 women and 425 men with cancer of the thyroid and, respectively, 3248 and 928 control subjects, odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were obtained by conditional regression models, conditioning on study and age at diagnosis, and adjusting for age and radiotherapy.
Results: A history of hypothyroidism was not associated with cancer risk (pooled ORs = 0.9, 95% confidence interval, CI: 0.7–1.3 in women and 1.7, 95% CI: 0.3–11.7 in men). ORs for hyperthyroidism were 1.4 (95% CI: 1.0–2.1) in women and 3.1 (95% CI: 1.0–9.8) in men. In women, however, risk was lower in the absence of or after allowance for history of goiter. Pooled ORs for a history of goiter were 5.9 (95% CI: 4.2–8.1) in women and 38.3 (95% CI: 5.0–291.2) in men. Risk for a history of benign nodules/adenomas was especially high (OR = 29.9, 95% CI: 14.5–62.0, in women; 18 cases *versus* 0 controls in men). The excess risk for goiter and benign nodules/adenomas was greatest within 2–4 years prior to thyroid cancer diagnosis, but an elevated OR was present 10 years or more before cancer.
Conclusions: Goiter and benign nodules/adenomas are the strongest risk factors for thyroid cancer, apart from radiation in childhood.

Introduction

Thyroid cancer is a relatively rare form of cancer, world standardized incidence rates in developed countries being approximately 2–3 per 100,000 males and 4–8 per 100,000 females [1]. Five-year relative survival rates for this malignancy vary greatly according to histologic type, ranging from 98% for papillary carcinoma and

92% for follicular carcinoma to 11% for anaplastic carcinoma [2]. In the past three decades, mortality rates for thyroid cancer have been slowly decreasing, while incidence rates have increased in most developed countries [3]. Trends in incidence are, however, difficult to interpret since they are influenced by changes in diagnostic criteria (*i.e.* increasing emphasis on cytological rather than architectural features), and the use of more accurate diagnostic techniques (*i.e.* fine-needle biopsy, scintigraphy and ultrasound) [4].

As with thyroid cancer, the classification of benign thyroid diseases is complex and has changed substantially since the introduction of the diagnostic techniques mentioned above, as well as radioimmunoassay tests for the determination of serum thyroxin, triiodothyronine, thyrotropin, and thyroid autoantibodies. As a consequence, thyroid-hormone deficit (hypothyroidism) or excess (hyperthyroidism), goiter, and benign nodules or adenomas have been found to be more common than was previously thought, especially among women during their reproductive period [5–8]. Genetic factors, lifestyle (including medical ascertainment), hormonal factors, and radiation are associated with the development of benign [9], as well as malignant, thyroid nodules [10, 11].

Iodine-deficient goiter is thought to be involved in the development of thyroid cancer because thyroid cancer mortality rates are high in mountainous areas such as the Alps, Andes, and Himalayas, where severe iodine deficiency was or still is common [10, 12]. Induction of thyroid carcinoma with a low-iodine diet (either alone or in combination with an initiator) has been reported in rats, mice, and hamsters [13]. The eradication of endemic goiter in most developed countries has been accompanied by decreases in the frequency of follicular and anaplastic carcinomas, making papillary carcinoma the predominant histological type [3, 14].

Several case–control studies from Europe, the United States, and China have reported odds ratios (ORs) of thyroid cancer around 5 for goiter and over 10 for benign thyroid nodules [15–22]. The role of hypothyroidism and hyperthyroidism in the etiology of thyroid cancer is less clear [10, 23]. Although most results are consistent, each of the studies was hindered by the relatively small numbers of cases and controls. In addition, the history of benign thyroid diseases was analyzed differently in most studies, making comparisons difficult. Thus, a pooled analysis should result in more precise risk estimates and a better understanding of the role of potential confounding and modifying factors (*e.g.* age, sex, area of residence, and time interval between benign and malignant thyroid disease).

Methods

Fourteen studies were identified through MEDLINE searches or personal knowledge of authors (Table 1). A detailed description of the studies included in this pooled analysis is given in a separate paper [24]. Briefly, four studies were conducted in the United States, including one in Los Angeles [16], one in Western Washington [15], one in Hawaii [19], and one in Connecticut [18]. Two were conducted in Asia, one in Hiroshima and Nagasaki, Japan (Ron, personal communication), and the other in Shanghai, China [17]. Of the eight European studies, five were conducted in Scandinavian countries, three in Sweden [21, 25, 26], and two in Norway [25, 27]. The remaining three were from northern Italy [22], the Swiss canton of Vaud [20], and Athens, Greece [28]. The studies by Glattre *et al.* [27] and Linos *et al.* [28] could not contribute to the present analyses since they did not include information on benign thyroid diseases.

Cases therefore totalled 2094 women and 425 men with cancer of the thyroid. Controls comprised 3248 females and 928 males (Table 1). About 80% of the thyroid cancers were papillary. Other histologic types included follicular carcinomas (15%), medullary carcinomas (2%), anaplastic carcinomas (0.7%), and cancers of undefined histology (3%). The median ages for cases and controls were 42 and 43 years among females, and 49 and 45 among males, but age ranges varied considerably across studies (Table 1).

The original datasets were restructured according to a predefined format and analyzed in a standardized way. The variables considered were history of and age at first diagnosis of hypothyroidism, hyperthyroidism, goiter and benign nodules/adenomas of the thyroid. Information on certain diseases was missing in a few studies (Figures 1–4). To rule out a spurious association due to increased case-findings at the time of diagnosis of benign thyroid diseases, these were included only if they had been diagnosed 1 year or more prior to diagnosis of thyroid cancer. Some information on treatment of benign thyroid diseases was reported in seven studies (*i.e.* those from the United States, Japan, Uppsala, and Tromsø). Data included in the present analysis (*e.g.* number of exposed subjects) may slightly differ from published ones, because exposure definitions or selection criteria were modified to maintain uniformity across studies.

For each benign thyroid disease, odds ratios (OR) were computed for individual studies using conditional-logistic regression [29]. For individually matched studies, where age was one of the matching variables, the original matching was used to define strata, while

Table 1. Age range and number of thyroid cancer cases and controls by study and gender

Location [ref.]	Age range (years)	Females			Males		
		Thyroid cancer cases		Controls	Thyroid cancer cases		Controls
		All	(Papillary)		All	(Papillary)	
America (USA)							
1. Los Angeles [16]	15–55	292	(243)	292	–	–	–
2. Western Washington [15]	18–80	185	(129)	393	–	–	–
3. Hawaii [19]	16–80	140	(115)	328	51	(47)	113
4. Connecticut [18]	20–76	109	(88)	208	50	(35)	76
Asia							
5. Hiroshima and Nagasaki, Japan	23–74	307	(284)	307	58	(51)	58
6. Shanghai, China [17]	18–54	207	(173)	207	–	–	–
Europe – North							
7. Southeastern Sweden [21]	21–60	149	(117)	187	26	(16)	200
8. Uppsala, Sweden [25]	17–72	133	(111)	203	37	(31)	54
9. Northern Sweden [26]	22–71	123	(93)	240	48	(34)	85
10. Norway, NHHS [27]	11–64	71	(45)	355	21	(17)	105
11. Tromsø, Norway [25]	20–72	58	(50)	138	24	(23)	58
Europe – South							
12. Northern Italy [22]	16–72	291	(210)	427	108	(64)	190
13. Vaud, Switzerland [20]	12–72	100	(75)	318	23	(19)	94
14. Athens, Greece [28]	14–88	82	(58)	96	32	(21)	44
Total		2247	(1791)	3699	478	(358)	1077
Subjects included in subsequent analyses*		2094	(1688)	3248	425	(320)	928

* Data on benign thyroid diseases not available for Refs [27] and [28].

quinquennia of age were used for other studies. In the Japanese study, cases and controls were also matched on A-bomb exposure and radiation dose. For Hawaii, the model also was conditioned on ethnicity. To account for possible imbalances in the age distribution of cases and controls within the 5-year age categories used for matching, three additional continuous terms for age (≤ 35, 36–55, ≥ 56) were included in the logistic models. After individual study analyses were completed, the studies were pooled, and conditional-logistic regression was used to estimate pooled ORs, conditioning on study. All analyses were adjusted for history of radiotherapy.

In the presence of very few or no controls with history of benign thyroid diseases (chiefly benign nodules/adenomas) in some strata, ORs and 95% confidence intervals (CIs) were computed, respectively, by means of unconditional-logistic regression or Fisher's exact test, after stratification and adjustment for study and age group, as appropriate [29]. For females, analyses could also be conducted in separate strata of study, histologic type (papillary – including mixed papillary/follicular – and follicular), geographical area (United States, Asia, Europe–North, Europe–South), and study design (three groups). The three major study designs were: (a) studies with population controls (the four American studies, the Chinese one, and the studies conducted in Uppsala, Sweden and Tromsø, Norway); (b) studies with hospital controls (northern Italy and Switzerland); and (c) studies with prevalent cases (those conducted in Japan, and southeastern and northern Sweden).

To test for heterogeneity across studies, geographic areas, study designs, and age categories (≤ 35, 36–55, ≥ 56 years), we used the likelihood ratio test and compared the model parameterized with a common OR to the model with stratum-specific ORs. Since tests for heterogeneity across geographic areas and study design were similar, we have reported only the former.

For each benign thyroid disease in females, a graph was given, in which a square was plotted for every study whose center projection on the underlying scale corresponded to the estimated OR. The area of the square was proportional to the inverse of the variance of the estimated risk parameter (logarithm of OR) [30].

Results

The relation between history of various benign thyroid diseases and thyroid cancer risk, by study and in the

STUDY [a]	EVER Cases/Controls	NEVER Cases/Controls	OR & 95% CI [b]	
AMERICA – USA				
292 Los Angeles	41/35	251/257	1.2	0.7 – 2.0
185 Western Washington	15/59	165/327	0.4	0.2 – 0.8
140 Hawaii	4/20	131/308	0.6	0.2 – 1.7
109 Connecticut	7/13	98/193	1.1	0.4 – 2.8
ASIA				
307 Japan	2/1	305/306	1.8	0.2 – 20.2
207 China	0/0	207/207	.	–
EUROPE – NORTH				
133 Uppsala – Sweden	3/1	115/198	2.9	0.3 – 33.3
58 Tromsø – Norway	3/4	47/130	2.3	0.4 – 11.6
EUROPE – SOUTH				
291 Northern Italy	6/5	285/422	1.9	0.6 – 6.4
100 Switzerland	1/3	99/315	1.2	0.1 – 12.3
Total:	**82/141**	**1703/2663**	**0.9**	**0.7 – 1.3**

Test for heterogeneity between studies: χ^2 (8 d.f.) = 10.80; P = 0.21

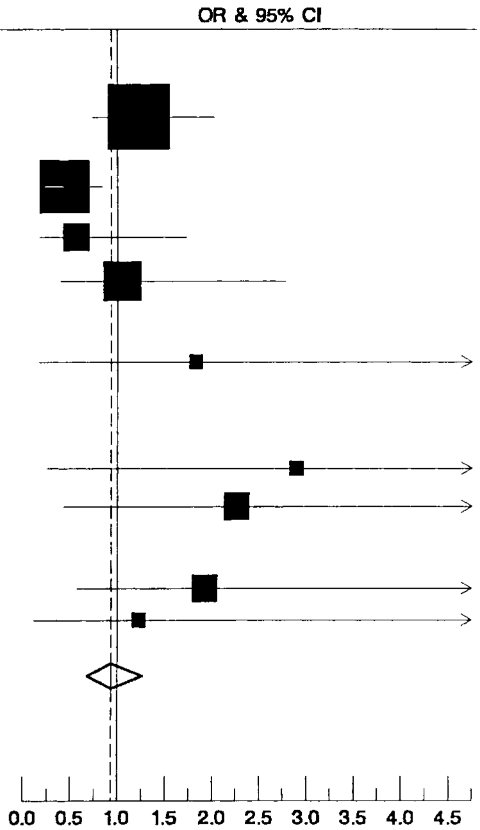

Fig. 1. Relationship between history of hypothyroidism and thyroid cancer by study and overall in females. [a] Studies in each area sorted by number of cases. [b] Estimates from conditional-logistic regression, conditioned on study and age, and adjusted for age and history or radiotherapy. OR = odds ratio; CI = confidence interval.

total sample, in females is shown in Figures 1 through 4. Corresponding ORs in the total male sample are given in Table 2.

A history of hypothyroidism among control women ranged from 0.3% (Japan) to 15% (western Washington) (Figure 1), and occurred in 0.3% of control men (Table 2). The highest prevalences in females (> 5%) were observed in studies from the United States. In four studies, ORs around 2 were found, but in none of the studies was the direct association between hypothyroidism and cancer risk significant. The pooled ORs (0.9, 95% CI: 0.7–1.3 in females, Figure 1, and 1.7, 95% CI: 0.3–11.7 in males, Table 2) were not significantly heterogeneous. ORs for hypothyroidism in females by years since diagnosis, and strata by histologic type, geographic area, and age group are shown in Table 3. No significant heterogeneity was found, but studies from the United States tended to show systematically lower ORs. Use of synthetic thyroid hormones was reported by about 78% of women with hypothyroidism in North American studies, but the corresponding information was not available for most studies elsewhere.

History of hyperthyroidism was reported by 1–4% of female controls (Figure 2) and around 0.6% of male controls (Table 2). Elevated ORs were found in the studies from Los Angeles, United States; China; Uppsala, Sweden; and northern Italy, but not in other areas. The pooled ORs were 1.4 (95% CI: 1.0–2.1) in females (Figure 2) and 3.1 (95% CI: 1.0–9.8) in males (Table 2), *i.e.* not significantly heterogeneous. ORs for hyperthyroidism in females by years since diagnosis, and strata by histologic type, geographic area, and age group are shown in Table 4. For each histologic type and overall, ORs greater than 4.0 were found within 2 years prior to thyroid cancer diagnosis (Table 4). A significant heterogeneity was found across age groups, with decreasing OR with an increasing age at diagnosis (OR in women ≥ 56 years = 0.4; 95% CI: 0.2–0.9).

STUDY [a]	EVER Cases/Controls	NEVER Cases/Controls	OR & 95% CI [b]	
AMERICA – USA				
292 Los Angeles	14/8	278/284	2.1	0.8 – 5.9
185 Western Washington	0/4	180/382	0.0 [c]	0.0 – 2.1
140 Hawaii	4/14	133/314	0.8	0.2 – 2.9
109 Connecticut	4/7	102/200	1.2	0.3 – 4.3
ASIA				
307 Japan	4/4	303/303	1.2	0.3 – 4.8
207 China	5/0	202/207	∞ [c]	1.3 – ∞
EUROPE – NORTH				
149 Southeastern Sweden	1/1	137/165	0.5	0.0 – 8.6
133 Uppsala – Sweden	5/2	120/198	4.4	0.8 – 23.2
123 Northern Sweden	4/6	119/234	1.0	0.3 – 3.8
58 Tromsø – Norway	2/3	50/129	0.4	0.0 – 5.1
EUROPE – SOUTH				
291 Northern Italy	12/5	279/422	3.5	1.2 – 10.1
100 Switzerland	3/6	97/312	1.7	0.4 – 7.2
Total:	**58/60**	**2000/3150**	**1.4**	**1.0 – 2.1**

Test for heterogeneity between studies: χ^2 (9 d.f.) = 7.61; P = 0.57

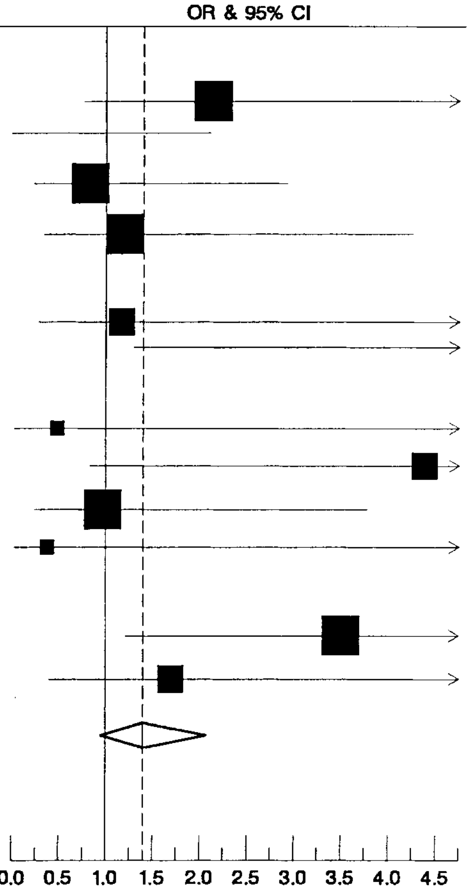

Fig. 2. Relationship between history of hyperthyroidism and thyroid cancer by study overall in females. [a] Studies in each area sorted by number of cases. [b] Estimates from conditional-logistic regression, conditioned on study and age, and adjusted for age and history or radiotherapy. [c] Confidence interval based on Fisher exact test. OR = odds ratio; CI = confidence interval.

A history of goiter was reported by 1–2% of control women in most studies, but by 6% in Switzerland (Figure 3). Goiter was rare among male controls (0.1%) (Table 2). ORs above 5.0 were found in most studies. Pooled ORs were 5.9 (95% CI: 4.2–8.1) in females (Figure 3) and 38.3 (95% CI: 5.0–291.2) in males (Table 2), *i.e.* significantly heterogeneous. ORs in females in specific strata by histologic type and geographic area were generally compatible with each other, but more than 10-fold increases were observed within 4 years prior to cancer diagnosis (Table 5). There was a tendency for the ORs to decline with age at cancer diagnosis. Four out of 76 female cases and 0 out of 121 female controls below age 21 at cancer diagnosis or interview reported a history of goiter. In subjects reporting goiter, the condition had been diagnosed below age 21 in 23% of cases and 25% of controls.

History of benign nodules/adenomas was reported by about 0.3–0.6% of control women (Figure 4). It was associated with grossly elevated risk in all studies. The pooled ORs were 29.9 (95% CI: 14.5–62.0) in females (Figure 4) and infinity in males (Table 2). Eighteen male cases and no controls with benign nodules/adenomas were found and the lower 95% confidence limit was 9.2. An approximately 20-fold elevated risk of thyroid cancer remained even 10 or more years after the diagnosis of benign nodules/adenomas (Table 6). The OR seemed higher for thyroid cancer of follicular than papillary type, but did not vary significantly across geographical areas. There was a significant heterogeneity between age groups with women age 56 or more showing a somewhat less elevated risk (9.1, 95% CI: 3.2–26.1) than younger ones (Table 6). Among women below age 21 at cancer diagnosis or at the time of interview, four out of 69 cases and none out of 107

STUDY [a]	EVER Cases/Controls	NEVER Cases/Controls	OR & 95% CI [b]	
AMERICA – USA				
292 Los Angeles	27/5	265/287	6.4	2.3 – 17.6
185 Western Washington	14/6	167/380	4.0	1.4 – 11.2
140 Hawaii	4/3	134/325	2.9	0.6 – 13.4
109 Connecticut	6/2	99/206	5.4	1.0 – 28.0
ASIA				
307 Japan	22/1	285/306	26.5	3.5 – 200.6
207 China	7/1	200/206	7.0	0.9 – 56.9
EUROPE – NORTH				
149 Southeastern Sweden	16/4	125/182	5.1	1.6 – 15.7
133 Uppsala – Sweden	24/5	105/196	6.9	2.6 – 18.3
58 Tromsø – Norway	8/3	47/132	5.3	1.2 – 23.6
EUROPE – SOUTH				
291 Northern Italy	25/7	266/420	5.8	2.4 – 13.7
100 Switzerland	25/19	75/299	6.8	3.4 – 13.7
Total:	178/56	1768/2939	5.9	4.2 – 8.1

Test for heterogeneity between studies: χ^2 (10 d.f.) = 3.89; P = 0.95

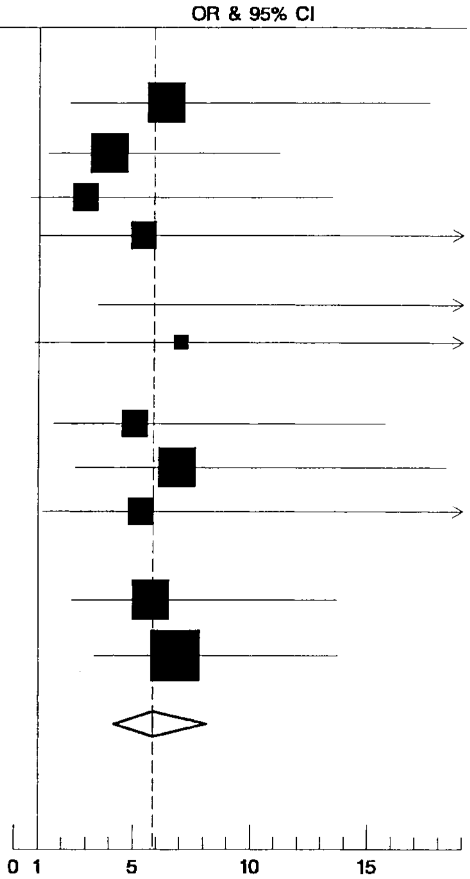

Fig. 3. Relationship between history of goiter and thyroid cancer by study and overall in females. [a] Studies in each area sorted by number of cases. [b] Estimates from conditional-logistic regression, conditioned on study and age, and adjusted for age and history or radiotherapy. OR = odds ratio; CI = confidence interval.

controls reported history of benign nodules/adenomas. In 11% of the cases but no control subjects with a history of benign nodules/adenomas, the disease was diagnosed below age 21.

Among females, 50 of 343 cases, with a history of any of the benign thyroid diseases considered, reported more than one condition; the corresponding numbers are 17 and 217 among controls. The thyroid conditions most frequently reported together (although not necessarily at the same time) were goiter and hyperthyroidism or hypothyroidism (Table 7). A history of hyperthyroidism in the absence of, or adjusted for, history of goiter was not associated to increased thyroid cancer risk (goiter-adjusted OR = 1.1; 95% CI: 0.7–1.7). ORs for goiter were not substantially affected by the presence of hyperthyroidism.

Among women without a history of goiter, those who suffered from hypothyroidism had an OR of 0.9 (95% CI: 0.6–1.2). However, the combined effect of hypothyroidism and goiter showed a negative departure from additivity. Goiter seemed associated with a significantly smaller increase in risk of thyroid cancer in the presence of hypothyroidism than in the absence of such a condition.

A history of benign nodules/adenomas coexisted with hypothyroidism in 12 cases and one control and with hyperthyroidism in nine cases and two controls. Goiter and benign nodules/adenomas were reported by nine cases and one control. No male controls and only four male cases reported a history of more than one benign thyroid condition.

Discussion

This pooled analysis of individual data from 12 case–control studies, conducted in seven countries, provides

STUDY [a]		EVER Cases/Controls	NEVER Cases/Controls	OR & 95% CI [b]	
AMERICA – USA					
292	Los Angeles	39/1	253/291	44.0	5.8 – 330.8
185	Western Washington	6/1	174/385	9.6	1.1 – 85.4
140	Hawaii	1/0	139/328	∞ [c]	0 – ∞
109	Connecticut	24/1	82/207	54.2	7.2 – 408.9
ASIA					
307	Japan	4/1	303/306	5.5	0.5 – 56.9
207	China	30/1	177/206	30.0	4.1 – 220.0
EUROPE – SOUTH					
291	Northern Italy	29/1	262/426	47.9	6.5 – 354.0
100	Switzerland	15/2	85/316	34.0	7.2 – 160.9
	Total:	148/8	1475/2465	29.9	14.5 – 62.0

Test for heterogeneity between studies: χ^2 (6 d.f.) = 3.72; P = 0.71

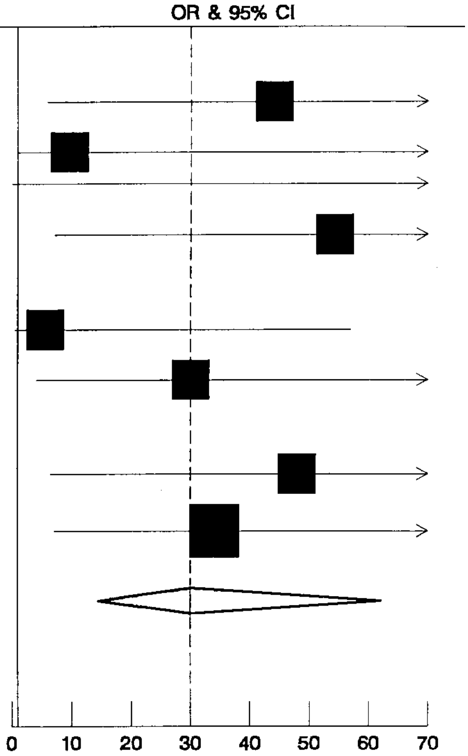

Fig. 4. Relationship between history of benign nodules/adenomas and thyroid cancer by study and overall in females. [a] Studies in each area sorted by number of cases. [b] Estimates from conditional-logistic regression, conditioned on study and age, and adjusted for age and history or radiotherapy. [c] Confidence interval based on Fisher exact test. OR = odds ratio; CI = confidence interval.

more precise estimates than previously available on the relationship between benign thyroid diseases and thyroid cancer (mostly well-differentiated, non-medullary carcinomas). It indicates that women with a history of goiter have an approximate 6-fold increased risk, and those with a history of benign nodules/adenomas have an approximate 30-fold increased risk for thyroid cancer. The excess risk was greatest within 2–4 years prior to thyroid cancer diagnosis, but elevated ORs were also present 10 years or more prior to diagnosis. Thus, increased case-finding during surgery or initial evaluation of benign conditions should not account for the strong and consistent associations observed with goiter and benign nodules/adenomas.

This study suggests that hypo- or hyperthyroidism are not associated with any substantial risk increase for thyroid cancer, particularly after allowance for a history of goiter. In a large series of hyperthyroid patients followed up for nearly a lifetime [23], thyroid cancer mortality rates were not increased in patients treated with antithyroid drugs or surgery. Information on incident data was not available [23]. A moderate increase in thyroid cancer mortality was found in patients treated with ^{131}I, but was more pronounced in patients with toxic nodular goiter (RR = 6.5) than those with less severe hyperthyroidism (RR = 2.1). Unfortunately, information on treatment of benign thyroid diseases was, in most pooled studies, absent or insufficient. Large inter-country differences in the prevalence of hypo- and hyperthyroidism emerged, however, pointing to substantial variability in the diagnostic criteria and medical surveillance of these benign thyroid conditions [7, 8].

An inverse association between history of hyperthyroidism and thyroid cancer in older women had not previously been reported. Although the possibility that this finding is due to chance or bias cannot be ruled out, hyperthyroidism may decrease risk through weight loss. In fact, obesity is associated with thyroid cancer risk in postmenopausal women [18, 31].

The associations with goiter and benign nodules/adenomas were consistent in specific subgroups of women. Increased risks were comparable for papillary

Table 2. Relationship between history of benign thyroid diseases and thyroid cancer risk in males

Benign thyroid disease	Ever Cases : controls	Never Cases : controls	OR*	(95% CI)
Hypothyroidism	3 : 2	337 : 634	1.7	(0.3–11.7)
Hyperthyroidism	9 : 5	406 : 899	3.1	(1.0–9.8)
Goiter	20 : 1	349 : 835	38.3	(5.0–291.2)
Benign nodules/adenomas	18 : 0	270 : 531	∞	(9.2–∞)†

* Estimates from conditional-logistic regression, conditioned on study and age, and adjusted for age and history of radiotherapy.
† CI based on Fisher exact text.
OR = odds ratio.
CI = confidence interval.

Table 3. ORs and corresponding 95% CIs* of thyroid cancer by history of hypothyroidism and selected characteristics in females

<table>
<tr><th rowspan="3">Characteristic</th><th>Affected</th><th colspan="6">OR (95% CI)</th></tr>
<tr><th rowspan="2">Cases : controls†</th><th rowspan="2">Never</th><th rowspan="2">Ever</th><th colspan="4">Years since diagnosis</th></tr>
<tr><th>1–2</th><th>3–4</th><th>5–9</th><th>≥10</th></tr>
<tr><td>All histologies</td><td>82 : 141</td><td>1</td><td>0.9 (0.7–1.3)</td><td>1.7 (0.8–4.0)</td><td>0.7 (0.2–2.5)</td><td>0.9 (0.5–1.9)</td><td>0.8 (0.6–1.2)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">χ^2 (trend) 1.77; 1 d.f.‡ p = 0.18</td></tr>
<tr><td>Papillary type</td><td>65 : 134</td><td>1</td><td>0.9 (0.7–1.3)</td><td>2.4 (0.9–6.4)</td><td>1.0 (0.3–3.3)</td><td>1.2 (0.6–2.4)</td><td>0.7 (0.5–1.1)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">χ^2 (trend) 4.65; 1 d.f. p = 0.03</td></tr>
<tr><td>Follicular type</td><td>14 : 94</td><td>1</td><td>0.7 (0.4–1.4)</td><td colspan="2">0.2 (0.0–1.8)</td><td colspan="2">0.9 (0.4–1.8)</td></tr>
<tr><td colspan="8">Area: All histologies</td></tr>
<tr><td>America (USA)</td><td>67 : 127</td><td>1</td><td>0.8 (0.6–1.1)</td><td colspan="2">0.7 (0.3–1.7)</td><td>0.8 (0.4–1.7)</td><td>0.8 (0.5–1.2)</td></tr>
<tr><td>Asia</td><td>2 : 1</td><td>1</td><td>1.8 (0.2–20.2)</td><td colspan="2">–</td><td colspan="2">1.8 (0.2–20.2)</td></tr>
<tr><td>Europe–North</td><td>6 : 5</td><td>1</td><td>2.4 (0.6–9.3)</td><td colspan="2">6.8 (0.7–67.8)</td><td colspan="2">1.0 (0.2–6.9)</td></tr>
<tr><td>Europe–South</td><td>7 : 8</td><td>1</td><td>1.7 (0.6–4.8)</td><td colspan="2">3.0 (0.8–11.6)</td><td colspan="2">0.7 (0.1–4.1)</td></tr>
<tr><td colspan="8">χ^2 heterogeneity between areas 4.2; 3 d.f. p = 0.24</td></tr>
<tr><td colspan="8">Area: Papillary type</td></tr>
<tr><td>America (USA)</td><td>52 : 121</td><td>1</td><td>0.8 (0.5–1.2)</td><td colspan="2">0.9 (0.3–2.4)</td><td>1.0 (0.4–2.2)</td><td>0.7 (0.5–1.1)</td></tr>
<tr><td>Asia</td><td>2 : 1</td><td>1</td><td>1.8 (0.2–20.2)</td><td colspan="2">–</td><td colspan="2">1.8 (0.2–20.2)</td></tr>
<tr><td>Europe–North</td><td>5 : 4</td><td>1</td><td>2.4 (0.5–11.3)</td><td colspan="2">6.8 (0.7–67.5)</td><td colspan="2">0.6 (0.1–7.7)</td></tr>
<tr><td>Europe–South</td><td>6 : 8</td><td>1</td><td>2.0 (0.6–6.1)</td><td colspan="2">3.9 (0.9–17.5)</td><td colspan="2">0.9 (0.2–5.0)</td></tr>
<tr><td colspan="8">χ^2 heterogeneity between areas 4.0; 3 d.f. p = 0.26</td></tr>
<tr><td colspan="8">Age: All histologies</td></tr>
<tr><td>≤35</td><td>33 : 43</td><td>1</td><td>1.1 (0.7–1.9)</td><td>1.6 (0.5–5.1)</td><td>1.4 (0.2–8.6)</td><td>1.6 (0.7–3.9)</td><td>0.7 (0.3–1.6)</td></tr>
<tr><td>36–55</td><td>39 : 68</td><td>1</td><td>1.0 (0.6–1.4)</td><td colspan="2">1.5 (0.4–5.0)</td><td>0.4 (0.1–1.9)</td><td>1.0 (0.6–1.7)</td></tr>
<tr><td>≥56</td><td>10 : 30</td><td>1</td><td>0.6 (0.3–1.3)</td><td colspan="2">0.7 (0.1–3.5)</td><td>0.3 (0.0–3.6)</td><td>0.5 (0.2–1.4)</td></tr>
<tr><td colspan="8">χ^2 heterogeneity between age groups 2.4; 2 d.f. p = 0.31</td></tr>
<tr><td colspan="8">Age: Papillary type</td></tr>
<tr><td>≤35</td><td>29 : 42</td><td>1</td><td>1.2 (0.7–2.0)</td><td>2.0 (0.6–7.0)</td><td>1.8 (0.3–11.2)</td><td>1.7 (0.7–4.4)</td><td>0.7 (0.3–1.6)</td></tr>
<tr><td>36–55</td><td>29 : 62</td><td>1</td><td>1.0 (0.6–1.7)</td><td colspan="2">2.8 (0.7–11.3)</td><td>0.7 (0.1–3.4)</td><td>0.9 (0.5–1.6)</td></tr>
<tr><td>≥56</td><td>7 : 30</td><td>1</td><td>0.5 (0.2–1.3)</td><td colspan="2">0.5 (0.1–4.1)</td><td colspan="2">0.4 (0.2–1.2)</td></tr>
<tr><td colspan="8">χ^2 heterogeneity between age groups 2.9; 2 d.f. p = 0.24</td></tr>
</table>

* Estimates from conditional-logistic regression conditioned on study and age, and adjusted for age and history of radiotherapy.
† Due to matching procedures, some controls could not be used.
‡ d.f. = Degrees of freedom.
OR = odds ratio; CI = confidence interval.

and follicular carcinomas, although these two most common types of well-differentiated thyroid cancer differ with respect to age and diagnostic pattern (*i.e.* papillary carcinoma is more often found in young individuals compared to follicular carcinoma) [4] and, possibly, etiology (*e.g.* iodine deficiency may selectively

Table 4. ORs and corresponding 95% CIs* of thyroid cancer by history of hyperthyroidism and selected characteristics in females

<table>
<tr><th rowspan="3">Characteristic</th><th>Affected</th><th colspan="6">OR (95% CI)</th></tr>
<tr><th rowspan="2">Cases : controls†</th><th rowspan="2">Never</th><th rowspan="2">Ever</th><th colspan="4">Years since diagnosis</th></tr>
<tr><th>1–2</th><th>3–4</th><th>5–9</th><th>≥10</th></tr>
<tr><td>All histologies</td><td>58 : 60</td><td>1</td><td>1.4 (1.0–2.1)</td><td>5.5 (1.9–15.5)</td><td>1.5 (0.4–6.2)</td><td>1.5 (0.6–3.4)</td><td>0.9 (0.5–1.6)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">*χ^2 (trend) 8.83; 1 d.f.‡ $p < 0.01$*</td></tr>
<tr><td>Papillary type</td><td>47 : 59</td><td>1</td><td>1.4 (0.9–2.1)</td><td>5.0 (1.7–14.5)</td><td>1.3 (0.3–5.9)</td><td>1.5 (0.6–3.5)</td><td>0.9 (0.5–1.7)</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">*χ^2 (trend) 6.78; 1 d.f. $p < 0.01$*</td></tr>
<tr><td>Follicular type</td><td>11 : 41</td><td>1</td><td>1.6 (0.8–3.6)</td><td colspan="2">5.0 (1.2–20.1)</td><td colspan="2">1.1 (0.4–3.0)</td></tr>
<tr><td colspan="8">**Area: All histologies**</td></tr>
<tr><td>America (USA)</td><td>22 : 33</td><td>1</td><td>0.9 (0.5–1.6)</td><td colspan="2">2.7 (0.8–9.8)</td><td colspan="2">0.6 (0.3–1.2)</td></tr>
<tr><td>Asia</td><td>9 : 4</td><td>1</td><td>2.5 (0.8–8.4)</td><td colspan="2">–</td><td colspan="2">2.5 (0.8–8.4)</td></tr>
<tr><td>Europe–North</td><td>12 : 12</td><td>1</td><td>1.3 (0.6–3.1)</td><td colspan="2">5.1 (1.0–25.9)</td><td colspan="2">0.7 (0.2–2.1)</td></tr>
<tr><td>Europe–South</td><td>15 : 11</td><td>1</td><td>2.7 (1.2–6.0)</td><td colspan="2">4.4 (0.8–23.3)</td><td colspan="2">2.3 (0.9–5.8)</td></tr>
<tr><td colspan="8">*χ^2 heterogeneity between areas 5.5; 3 d.f. $p = 0.14$*</td></tr>
<tr><td colspan="8">**Area: Papillary type**</td></tr>
<tr><td>America (USA)</td><td>19 : 33</td><td>1</td><td>0.9 (0.5–1.7)</td><td colspan="2">3.4 (1.0–12.1)</td><td colspan="2">0.5 (0.2–1.1)</td></tr>
<tr><td>Asia</td><td>9 : 3</td><td>1</td><td>3.2 (0.9–11.8)</td><td colspan="2">–</td><td colspan="2">3.2 (0.9–11.8)</td></tr>
<tr><td>Europe–North</td><td>8 : 12</td><td>1</td><td>1.1 (0.4–2.8)</td><td colspan="2">4.8 (0.9–25.4)</td><td colspan="2">0.5 (0.1–2.0)</td></tr>
<tr><td>Europe–South</td><td>11 : 11</td><td>1</td><td>2.7 (1.1–6.4)</td><td colspan="2">1.9 (0.3–13.5)</td><td colspan="2">2.9 (1.1–7.7)</td></tr>
<tr><td colspan="8">*χ^2 heterogeneity between areas 5.8; 3 d.f. $p = 0.12$*</td></tr>
<tr><td colspan="8">**Age: All histologies**</td></tr>
<tr><td>≤35</td><td>18 : 9</td><td>1</td><td>3.2 (1.4–7.7)</td><td colspan="2">4.0 (1.0–16.1)</td><td colspan="2">2.8 (0.9–8.5)</td></tr>
<tr><td>36–55</td><td>33 : 26</td><td>1</td><td>2.0 (1.2–3.5)</td><td colspan="2">20.7 (2.6–167.8)</td><td colspan="2">1.4 (0.7–2.5)</td></tr>
<tr><td>≥56</td><td>7 : 25</td><td>1</td><td>0.4 (0.2–0.9)</td><td colspan="2">0.3 (0.0–2.9)</td><td colspan="2">0.4 (0.1–1.0)</td></tr>
<tr><td colspan="8">*χ^2 heterogeneity between groups 19.1; 2 d.f. $p < 0.001$*</td></tr>
<tr><td colspan="8">**Age: Papillary type**</td></tr>
<tr><td>≤35</td><td>16 : 9</td><td>1</td><td>3.2 (1.3–8.2)</td><td colspan="2">3.6 (0.9–14.9)</td><td colspan="2">3.0 (0.9–10.1)</td></tr>
<tr><td>36–55</td><td>27 : 26</td><td>1</td><td>2.0 (1.1–3.6)</td><td colspan="2">18.2 (2.2–150.5)</td><td colspan="2">1.4 (0.7–2.6)</td></tr>
<tr><td>≥56</td><td>4 : 24</td><td>1</td><td>0.3 (0.1–0.9)</td><td colspan="2">0 (0.0–2.1)§</td><td colspan="2">0.4 (0.1–1.2)</td></tr>
<tr><td colspan="8">*χ^2 heterogeneity between groups 18.8; 2 d.f. $p < 0.001$*</td></tr>
</table>

* Estimates from conditional-logistic regression conditioned on study and age, and adjusted for age and history of radiotherapy.
† Due to matching procedures, some controls could not be used.
‡ d.f. = Degrees of freedom.
§ CI based on Fisher exact test.
OR = odds ratio; CI = confidence interval.

increase follicular carcinoma) [10]. Individuals with the lowest background incidence rates of thyroid cancer (*i.e.* men of all ages and women below age 36) showed the highest ORs. In clinical series, males have been reported to have higher prevalence of thyroid cancer in association with benign nodules/adenomas [32].

Lack of validation of diagnoses of benign thyroid diseases was a weakness of most studies and a possible source of bias if reporting of benign conditions was not equally accurate in cases and controls. However, the consistency of results on goiter and benign nodules/adenomas across populations and study designs, including from population-based studies and hospital-based ones (where there should be less recall bias) [29], is reassuring.

From a clinical viewpoint, goiter includes a rather broad range of conditions which differ by severity (simple and toxic goiter) and etiology (iodine deficiency, autoimmunity, drugs, *etc.*) [33]. Recently experienced severe iodine deficiency was unlikely in all study areas. Some subclinical iodine deficiency may have been present in Switzerland and Sweden where goiter endemicity existed before iodization of food supplies started in the 1920s [34] or 1930s [14], and, most notably, in some areas of Italy where iodized salt was never used widely [35]. Conversely, other study populations (*i.e.* Hawaii

Table 5. ORs and corresponding 95% CIs* of thyroid cancer by history of goiter and selected characteristics in females

Characteristic	Affected	OR (95% CI)					
	Cases : controls†	Never	Ever	Years since diagnosis			
				1–2	3–4	5–9	≥ 10
All histologies	178 : 56	1	5.9 (4.2–8.1)	13.7 (4.7–40.4)	15.3 (3.5–66.6)	6.7 (3.1–14.6)	4.2 (2.8–6.3)
						χ^2 (trend) 6.21; 1 d.f.‡ p = 0.01	
Papillary type	138 : 55	1	5.5 (3.9–7.8)	11.4 (3.7–35.3)	16.4 (3.7–72.4)	6.9 (3.1–15.2)	3.8 (2.4–5.9)
						χ^2 (trend) 5.82; 1 d.f. p = 0.02	
Follicular type	32 : 40	1	6.9 (3.8–12.4)	19.0 (4.9–73.5)	4.0 (0.1–126.3)	2.6 (0.4–17.9)	5.4 (2.6–11.3)
Area: All histologies							
America (USA)	51 : 16	1	4.4 (2.4–8.0)	21.0 (2.7–162.3)		12.6 (2.8–56.1)	1.7 (0.8–3.8)
Asia	29 : 2	1	16.5 (3.9–70.3)	∞ (0.00–∞)§		16.0 (3.8–68.3)	
Europe–North	48 : 12	1	5.9 (3.1–11.4)	21.6 (5.1–91.9)		2.1 (0.5–9.2)	2.4 (0.9–6.4)
Europe–South	50 : 26	1	6.1 (3.6–10.4)	5.9 (1.4–25.8)		5.1 (1.3–20.1)	6.4 (3.4–11.8)
χ^2 heterogeneity between areas 3.2; 3 d.f. p = 0.36							
Area: Papillary type							
America (USA)	43 : 15	1	4.8 (2.5–9.0)	21.7 (2.7–172.9)		13.6 (3.0–61.2)	1.8 (0.7–4.4)
Asia	27 : 2	1	17.2 (3.8–78.4)	∞ (0.0–∞)§		16.7 (3.7–76.0)	
Europe–North	35 : 12	1	4.8 (2.4–9.6)	19.9 (4.6–86.1)		1.6 (0.3–7.7)	1.5 (0.5–4.6)
Europe–South	33 : 26	1	5.6 (3.1–10.1)	4.3 (0.8–22.0)		5.5 (1.3–22.9)	5.9 (2.9–11.7)
χ^2 heterogeneity between areas 2.9; 3 d.f. p = 0.40							
Age: All histologies							
≤35	51 : 9	1	8.4 (4.0–17.5)	11.0 (3.2–38.1)		19.9 (2.6–155.0)	4.1 (1.4–12.2)
36–55	86 : 22	1	6.3 (3.8–10.4)	45.0 (5.9–345.6)		5.1 (1.9–13.7)	4.1 (2.2–7.8)
≥56	41 : 25	1	4.2 (2.4–7.4)	3.5 (0.6–21.2)		2.9 (0.4–21.3)	4.6 (2.4–8.7)
χ^2 heterogeneity between age groups 2.8; 2 d.f. p = 0.25							
Age: Papillary type							
≤35	44 : 9	1	8.1 (3.8–17.1)	10.5 (2.9–37.8)		18.4 (2.3–143.8)	4.0 (1.3–12.3)
36–55	69 : 21	1	6.1 (3.6–10.3)	39.6 (5.0–312.3)		5.8 (2.1–15.9)	3.7 (1.9–7.4)
≥56	25 : 25	1	3.4 (1.8–6.5)	3.0 (0.4–22.3)		1.8 (0.2–15.8)	3.9 (1.9–8.1)
χ^2 heterogeneity between age groups 3.6; 2 d.f. p = 0.17							

* Estimates from conditional-logistic regression conditioned on study and age, and adjusted for age and history of radiotherapy.
† Due to matching procedures, some controls could not be used.
‡ d.f. = Degrees of freedom.
§ CI based on Fisher exact test.
OR = odds ratio; CI = confidence interval.

and Japan) tend to have elevated iodine intake through water, fish, and seafood [36]. Even our pooled analysis had insufficient power to tackle interaction, but it suggested sub-additivity (or causal antagonism) for the joint effect of goiter and hypothyroidism but, possibly, some super-multiplicativity (or synergism) for goiter and hyperthyroidism.

No other known factor, except exposure to high-dose external radiation during childhood [11], is associated to risks for thyroid cancer comparable to those found for goiter and benign nodules/adenomas. From a prevention viewpoint, however, concealed among the large number of benign thyroid nodules there are only relatively few, mostly curable, thyroid cancers [37]. Thus, the extent to which benign thyroid diseases must be biopsied [37] or excised [38] is far from clear.

Acknowledgements

The authors thank Mrs Luigina Mei for editorial assistance. This work was conducted with contributions from the Italian Association for Research on Cancer and the National Cancer Institute, United States.

Table 6. ORs and corresponding 95% CI* of thyroid cancer by history of benign nodules/adenomas and selected characteristics in females

Characteristic	Affected	OR (95% CI)					
	Cases : controls†	Never	Ever	Years since diagnosis			
				1–2	3–4	5–9	≥10
All histologies	148 : 8	1	29.9 (14.5–62.0)	76.1 (10.4–557.7)	42.5 (5.7–318.0)	21.2 (6.2–72.2)	19.0 (5.8–62.9)
						χ^2 *(trend) 1.72; 1 d.f.*‡ *p = 0.19*	
Papillary type	115 : 8	1	28.9 (13.6–61.2)	75.4 (10.2–558.8)	44.2 (5.7–341.3)	18.9 (5.4–66.3)	17.3 (4.8–62.8)
						χ^2 *(trend) 1.92; 1 d.f. p = 0.17*	
Follicular type	27 : 5	1	62.3 (18.9–205.8)	91.4 (8.3–1010.8)		54.6 (14.2–210.2)	
Area: All histologies							
America (USA)	70 : 3	1	34.4 (10.6–111.2)	28.1 (6.6–119.4)		47.0 (6.3–351.5)	
Asia	34 : 2	1	18.4 (4.3–77.7)	∞ (4.6–∞)‡		9.5 (2.1–42.6)	
Europe–North§	– : –	–	–	– –	–	– –	
Europe–South	44 : 3	1	33.8 (10.3–110.7)¶	∞ (8.8–∞)‡		17.6 (5.2–59.0)¶	
χ^2 *heterogeneity between areas 0.5; 2 d.f. p = 0.79*							
Area: Papillary type							
America (USA)	54 : 3	1	30.2 (9.2–99.3)	26.2 (6.1–113.2)		38.4 (5.0–294.8)	
Asia	29 : 2	1	14.5 (3.5–60.8)	∞ (4.3–∞)‡		6.5 (1.5–28.8)	
Europe–North	– : –	–	–	– –	–	– –	
Europe South	32 : 3	1	36.6 (10.8–124.4)¶	∞ (10.0–∞)‡		17.3 (4.9–61.8)¶	
χ^2 *heterogeneity between areas 0.4; 2 d.f. p = 0.84*							
Age: All histologies							
≤35	62 : 2	1	49.2 (11.8–204.4)¶	67.8 (9.1–503.1)¶		30.9 (4.1–232.1)¶	
36–55	64 : 1	1	107.9 (14.8–785.1)¶	43.4 (5.8–326.0)¶		∞ (14.8–∞)‡	
≥56	22 : 5	1	9.1 (3.2–26.1)	∞ (3.1–∞)‡		5.6 (2.0–16.0)¶	
χ^2 *heterogeneity between age groups 7.3; 2 d.f. p = 0.03*							
Age: Papillary type							
≤35	55 : 2	1	49.3 (11.8–205.6)¶	64.8 (8.7–482.7)¶		34.1 (4.5–257.3)¶	
36–55	48 : 1	1	103.7 (14.1–762.2)¶	47.5 (6.2–362.4)¶		∞ (11.7–∞)‡	
≥56	12 : 5	1	8.3 (2.5–27.9)	∞ (3.0–∞)‡		3.9 (1.1–13.4)¶	
χ^2 *heterogeneity between age groups 8.8; 2 d.f. p = 0.01*							

* Estimates from conditional-logistic regression conditioned on study and age, and adjusted for age and history of radiotherapy.
† Due to matching procedures, some controls could not be used.
‡ CI based on Fisher exact test.
§ Data on benign nodules/adenomas not available.
¶ Estimates from unconditional logistic regression adjusted for study, age, and history of radiotherapy.
OR = odds ratio; CI = confidence interval.

Table 7. Combined effect of history of hyper- or hypothyroidism and goiter in females*

Condition	Goiter†				Adjusted also for goiter OR (95% CI)
	No		Yes		
	Ca : Co	OR (95% CI)	Ca : Co	OR (95% CI)	
Hyperthyroidism					
No	1725 : 2866	1	152 : 49	5.9 (4.2–8.4)	1
Yes	33 : 49	1.1 (0.7–1.7)	20 : 5	7.8 (2.8–21.5)	1.1 (0.7–1.7)
Adjusted also for hyperthyroidism		1		6.1 (4.3–8.5)	
Hypothyroidism					
No	1560 : 2619	1	141 : 44	6.7 (4.6–9.7)	1
Yes	66 : 133	0.9 (0.6–1.2)	16 : 8	3.5 (1.4–8.7)	0.8 (0.6–1.2)
Adjusted also for hypothyroidism		1		6.3 (4.4–8.8)	

* Studies in which data on goiter were not available were excluded (northern Sweden, Norway, and Greece).
† Estimates from conditional-logistic regression, conditioned on age, and adjusted for age and history of radiotherapy.
OR = odds ratio; CI = confidence interval.

References

1. Parkin DM, Whelan SL, Ferlay J, *et al.* (1997) *Cancer Incidence in Five Continents*, Vol. VII. IARC Scientific Publication No. 143. Lyon: International Agency for Research on Cancer.
2. Gilliland FD, Hunt WC, Morris DM, Key CR (1997) Prognostic factors for thyroid carcinoma. *Cancer* **79**: 564–573.
3. Franceschi S, La Vecchia C (1994) Thyroid cancer. *Cancer Surv* **19/20**: 393–421.
4. Correa P, Chen VW (1995) Endocrine gland cancer. *Cancer* **75** (Suppl. 1): 338–352.
5. Okamura K, Nakashima T, Ueda K, *et al.* (1987) Thyroid disorders in the general population of Hisayama, Japan, with special reference to prevalence and sex differences. *Int J Epidemiol* **16**: 545–549.
6. Tunbridge WMG, Evered DC, Hall R, *et al.* (1997) The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol* **7**: 481–493.
7. Lindsay RS, Toft AD (1997) Hypothyroidism. *Lancet* **349**: 413–417.
8. Lazarus JH (1997) Hyperthyroidism. *Lancet* **349**: 339–343.
9. Wong FL, Ron E, Gierlowski T, Schneider AB (1996) Benign thyroid tumors: general risk factors and their effects on radiation risk estimation. *Am J Epidemiol* **144**: 728–733.
10. Franceschi S, Boyle P, Maisonneuve P, *et al.* (1993) The epidemiology of thyroid carcinoma. *Crit Rev Oncol* **4**: 25–52.
11. Ron E, Lubin JH, Shore RE, *et al.* (1995) Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* **141**: 259–277.
12. Wegelin C (1928) Malignant disease of the thyroid gland and its relation to goitre in man and animals. *Cancer Rev* **3**: 297–313.
13. Yamashita H, Noguchi S, Murakami N, *et al.* (1990) Effects of dietary iodine on chemical introduction on thyroid carcinoma. *Acta Pathol Jpn* **40**: 705–712.
14. Petterson B, Coleman MP, Ron E, Adami H-O (1996) Iodine supplementation in Sweden and regional trends in thyroid cancer incidence by histopathologic type. *Int J Cancer* **65**: 13–19.
15. McTiernan AM, Weiss NS, Daling JR (1984) Incidence of thyroid cancer in women in relation to previous exposure to radiation therapy and history of thyroid disease. *J Natl Cancer Inst* **73**: 575–581.
16. Preston-Martin S, Bernstein L, Pike MC, Maldonado AA, Henderson BE (1987) Thyroid cancer among young women related to prior thyroid disease and pregnancy history. *Br J Cancer* **55**: 191–195.
17. Preston-Martin S, Jin F, Duda MJ, Mack WJ (1993) A case–control study of thyroid cancer in women under age 55 in Shanghai (People's Republic of China). *Cancer Causes Control* **4**: 431–440.
18. Ron E, Kleinerman RA, Boice JD, LiVolsi VA, Flannery JT, Fraumeni JF Jr (1987) A population-based case–control study of thyroid cancer. *J Natl Cancer Inst* **79**: 1–12.
19. Kolonel LN, Hankin JH, Wilkens LR, Fukunaga FH, Hinds MW (1990) An epidemiologic study of thyroid cancer in Hawaii. *Cancer Causes Control* **1**: 223–234.
20. Levi F, Franceschi S, La Vecchia C, *et al.* (1991) Previous thyroid disease and risk of thyroid cancer in Switzerland. *Eur J Cancer* **27**: 85–88.
21. Wingren G, Hatschek T, Axelson O (1993) Determinants of papillary cancer of the thyroid. *Am J Epidemiol* **138**: 482–491.
22. D'Avanzo B, La Vecchia C, Franceschi S, Negri E, Talamini R (1995) History of thyroid diseases and subsequent thyroid cancer risk. *Cancer Epidemiol Biomarkers Prev* **4**: 193–199.
23. Ron E, Doddy MM, Beckeer DV, *et al.* (1998) Cancer mortality following treatment for adult hyperthyroidism. *JAMA* **280**: 347–355.
24. Negri E, Ron E, Franceschi S, *et al.* (1999) A pooled analysis of case–control studies of thyroid cancer. I. Methods. *Cancer Causes Control* **10**: 131–142.
25. Galanti MR, Hansson L, Bergstrom R, *et al.* (1997) Diet and the risk of papillary and follicular thyroid carcinoma: a population-based case–control study in Sweden and Norway. *Cancer Causes Control* **8**: 205–214.
26. Hallquist A, Hardell L, Degerman A, Boquist L (1994) Thyroid cancer: reproductive factors, previous diseases, drug intake, family history and diet. A case–control study. *Eur J Cancer Prev* **3**: 481–488.
27. Glattre E, Haldorsen T, Berg JP, Stensvold I, Sovoll K (1993) Norwegian case–control study testing the hypotheses that seafood increases the risk of thyroid cancer. *Cancer Causes Control* **4**: 11–16.
28. Linos A, Linos DA, Vgotza N, Souvatzoglou A, Koutras DA (1989) Does coffee consumption protect against thyroid disease? *Acta Chir Scand* **155**: 317–320.

29. Breslow NE, Day NE (1980) *Statistical Methods in Cancer Research*. Vol. 1: *The Analysis of Case–Control Studies*. IARC Scientific Publication No. 32. Lyon: International Agency for Research on Cancer, 1980.
30. Collaborative Group on Hormonal Factors in Breast Cancer (1996) Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* **347**: 1713–1727.
31. Goodman MT, Kolonel LN, Wilkens LR (1992) The association of body size, reproductive factors and thyroid cancer *Br J Cancer* **66**: 1180–1184.
32. Belfiore A, La Rosa GL, La Porta GA, *et al*. (1992) Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multinodularity. *Am J Med* **93**: 363–369.
33. Wartofsky L (1994) Diseases of the thyroid. In: Isselbacher KJ, Braunwald E, Wilson JD, *et al*. eds. *Harrison's Principles of Internal Medicine*, Vol. 2, 13th edn. New York: McGraw-Hill, pp. 1930–1953.
34. Wynder EL (1952) Some practical aspects of cancer prevention (concluded). *N Engl J Med* **246**: 573–582.
35. Franceschi S, La Vecchia C, Bidoli E (1998) High incidence of thyroid cancer in central Italy. *Int J Cancer* **77**: 481–482.
36. Goodman MT, Yoshizawa CN, Kolonel LN (1988) Descriptive epidemiology of thyroid cancer in Hawaii. *Cancer* **61**: 1272–1281.
37. Mazzaferri EL (1992) Thyroid cancer in thyroid nodules: finding a needle in the haystack. *Am J Med* **93**: 359–362.
38. Wheeler MH (1998) Total thyroidectomy for benign thyroid disease. *Lancet* **351**: 1526–1527.